PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 11 April 2001 (11.04.01)	
International application No. PCT/US00/16243	**Applicant's or agent's file reference** A3321A-WO
International filing date (day/month/year) 13 June 2000 (13.06.00)	**Priority date** (day/month/year) 15 June 1999 (15.06.99)
Applicant HERPIN, Timothy, F. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

12 January 2001 (12.01.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer S. Mafla
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/16243

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.

US CL :435/7.1, 7.2; 436/501, 518; 514/255; 544/359, 360, 361, 362, 363

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/7.1, 7.2; 436/501, 518; 514/255; 544/359, 360, 361, 362, 363

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,880,128 A (DOLL et al) 09 March 1999, see entire document, especially columns 27-30 (Process D) and Examples 21, 22, 24-26.	1-4 --- 5-14
X --- Y	US 5,734,054 A (DOLLE, III et al) 31 March 1998, see entire document, especially Schemes 6 & 7 (columns 21-22).	1-6 --- 7-14
X --- Y	BREITENBUCHER et al. Generation of a Piperazine-2-carboxamide Library: A Practical Application of the Phenol-Sulfide React and Release Linker. Tet. Lett., 12 March 1998, Vol. 39, pp. 1295-1298, see entire article, espeically Scheme III (page 1296).	1-4 --- 5-14

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 23 AUGUST 2000	Date of mailing of the international search report 05 OCT 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MAURIE E. GARCIA Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet) (July 1998)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/16243

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,324,483 A (CODY et al) 28 June 1994, see Scheme 10 (columns 46-47) and Table 10 (columns 65-68).	1-14
Y	WO 98/58947 A1 (PFIZER INC.) 30 December 1998, see Schemes 7-9 (pages 75-77) and pages 158-159.	14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/16243

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

G01N 33/53, 33/566, 33/543; A01N 43/60; A61K 31/495; C07D 403/00, 401/00

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

WEST, STN (Registry, CAPlus, USPATfull, Scisearch, Medline, BIOSIS)
Search Terms: Structure search, combinatorial, library, solid phase, solid support/supported, piperazine, carbonyl, carboxy, diazacycloalkyl

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-6, drawn to a method of preparing compounds of a first formula.
Group II, claim(s) 7-13, drawn to a method of preparing compounds of a second formula.
Group III, claim(s) 14, drawn to a method of preparing compounds of a third formula.

The inventions listed as Groups I-III do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The groups lack the same or corresponding technical feature. The claims in each of the group are linked by the compounds that are made by each method. The structures of each of the compounds made is different. The compounds made by the method of Group I have carbonyl or sulfonyl on each nitrogen in the ring, while the compounds made by the method of Group II have only one of such substituents (the other is an aliphatic or aromatic group). The compounds made by the method of Group III contain a fused ring system that is not contemplated in either one of the other groups.

PCT Rule 13.2 states that unity of invention shall be fulfilled when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features". It further defines "special technical feature" as "those technical features that define a contribution which each of the claimed inventions, claimed as a whole, makes over the prior art". For example, unity of invention is fulfilled if:

(a) all alternatives have a common property; and

(b) (i) a common structure is present, i. e. a significant structural element is shared by all alternatives, or

(b) (ii) in cases where the common structure can not be the unifying criterion, all alternatives belong to a recognized class of compounds in the art to which the invention pertains. (MPEP Section 1850).

In the instant case, there is no showing that the claimed compounds would all have a common property. Even if so, the compounds do not possess a common structure as set forth above.

Further, the method of Group I (and the compounds made therefrom) is known in the art. See US 5,880,128 A to DOLL et al, issued 09 March 1999, Process D of the patent (in columns 27-30) and Examples 21, 22, 24-26, for example.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference A3321A-WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/16243	International filing date *(day/month/year)* 13 JUNE 2000	Priority date *(day/month/year)* 15 JUNE 1999
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant AVENTIS PHARMACEUTICALS PRODUCTS INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [X] Non-establishment of report with regard to novelty, inventive step or industrial applicability
   - IV [X] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

Date of submission of the demand	Date of completion of this report
12 JANUARY 2001	11 OCTOBER 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Dorthea Lawrence for MAURIE E. GARCIA Telephone No. (703) 308-0196

Form PCT/IPEA/409 (cover sheet) (July 1998) *

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/16243

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:
pages (See Attached) , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the claims:
pages (See Attached) , as originally filed
pages _____ , as amended (together with any statement) under Article 19
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the drawings:
pages (See Attached) , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the sequence listing part of the description:
pages (See Attached) , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE

☒ the claims, Nos. NONE

☒ the drawings, sheets/fig NONE

5. ☒ This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

***Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/16243

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application.

☒ claims Nos. 15

because:

☐ the said international application, or the said claim Nos. _ relate to the following subject matter which does not require international preliminary examination *(specify)*.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _ are so unclear that no meaningful opinion could be formed *(specify)*.

☐ the claims, or said claims Nos. _ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 15 .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/16243

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- [ ] restricted the claims.
- [X] paid additional fees.
- [ ] paid additional fees under protest.
- [ ] neither restricted nor paid additional fees.

2. [ ] This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- [ ] complied with.
- [X] not complied with for the following reasons:

Please See Supplemental Sheet.

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- [ ] all parts.
- [X] the parts relating to claims Nos. 1-14.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/16243

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	5-14	YES
	Claims	1-4	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-14	NO
Industrial Applicability (IA)	Claims	1-14	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Applicant's arguments filed 31 July 2001 have been fully considered but were not found persuasive.

First, the amendments to claims 1 and 7 have not been considered because they are deemed to be new matter. See MPEP 1878.02: In a situation where new matter is introduced by amendment in reply to a Written Opinion, the International Preliminary Examination Report will be established ***as if the amendment had not been made,*** and the report should so indicate. It shall also indicate the reasons why the amendment goes beyond the disclosure (PCT Rule 70.2(c)).

Thus the arguments directed at amended claims 1 and 7 are moot.

With respect to the arguments directed at the lack of inventive step for claims 1-6, 7-13 and 14:

The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

The examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

The examiner maintains that the claimed invention would have been prima facie obvious to one of ordinary skill in the art of combinatorial chemistry in view of the combined teachings of the cited references. Variation in protecting groups was known as set forth in the references. Variation (Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

CLASSIFICATION:
The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(7): G01N 33/53, 33/566, 33/543; A01N 43/60; A61K 31/495; C07D 403/00, 401/00 and US Cl.: 435/7.1, 7.2; 436/501, 518; 514/255; 544/359, 360, 361, 362, 363

I. BASIS OF REPORT:

This report has been drawn on the basis of the description,
page(s) 1-62, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the claims,
page(s) NONE, as originally filed.
page(s) NONE, as amended under Article 19.
page(s) NONE, filed with the demand.
and additional amendments:
Claim pages 63-67b filed with the letter of July 31, 2001.

This report has been drawn on the basis of the drawings,
page(s) NONE, as originally filed.
page(s) NONE, filed with the demand.
and additional amendments:
NONE

This report has been drawn on the basis of the sequence listing part of the description:
page(s) NONE, as originally filed.
pages(s) NONE, filed with the demand.
and additional amendments:
NONE

5. (Some) amendments are considered to go beyond the disclosure as filed:
With respect to claim 1: The claim has been amended to contain a negative proviso regarding the L group. Any negative limitation or exclusionary proviso must have basis in the original disclosure. Applicant points to pages 20-25 but there does not appear to be support for this negative limitation at the cited locations or anywhere else in the instant disclosure.

With respect to claim 7: The claim has been amended to contain a moiety denoted "Ha" (in new step (1)). Applicant points to pages 27 and 53 but there does not appear to be support for this limitation at the cited locations or anywhere else in the instant disclosure.

IV. LACK OF UNITY OF INVENTION:

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2, and 13.3 is not complied with for the following reasons:
As applicant was previously notified this International Preliminary Examining Authority has found plural inventions claimed in the International Application covered by the claims indicated below:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-6, drawn to a method of preparing compounds of a first formula.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Group II, claim(s) 7-13, drawn to a method of preparing compounds of a second formula.
Group III, claim(s) 14, drawn to a method of preparing compounds of a third formula.

and it considers that the International Application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated below:

The inventions listed as Groups I-III do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The groups lack the same or corresponding technical feature. The claims in each of the group are linked by the compounds that are made by each method. The structures of each of the compounds made is different. The compounds made by the method of Group I have carbonyl or sulfonyl on each nitrogen in the ring, while the compounds made by the method of Group II have only one of such substituents (the other is an aliphatic or aromatic group). The compounds made by the method of Group III contain a fused ring system that is not contemplated in either one of the other groups.

PCT Rule 13.2 states that unity of invention shall be fulfilled when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features". It further defines "special technical feature" as "those technical features that define a contribution which each of the claimed inventions, claimed as a whole, makes over the prior art". For example, unity of invention is fulfilled if:

(a) all alternatives have a common property; and

(b) (i) a common structure is present, i. e. a significant structural element is shared by all alternatives, or

(b) (ii) in cases where the common structure can not be the unifying criterion, all alternatives belong to a recognized class of compounds in the art to which the invention pertains. (MPEP Section 1850).

In the instant case, there is no showing that the claimed compounds would all have a common property. Even if so, the compounds do not possess a common structure as set forth above.

Further, the method of Group I (and the compounds made therefrom) is known in the art. See US 5,880,128 A to DOLL et al, issued 09 March 1999, Process D of the patent (in columns 27-30) and Examples 21, 22, 24-26, for example.

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):

of linking sites for structurally similar compounds were also known. Lastly, reaction of piperazines to make hydantoins was also known.

One of ordinary skill would have been motivated to perform solid phase synthesis and/or make libraries due to the known advantages in the art of such techniques.

A. Claims 1-4 lack novelty under PCT Article 33(2) as being anticipated by Doll et al.

Doll et al disclose a method of making carbonyl piperazinyl compounds on a solid support (see Abstract and Process D in columns 27-28). The compounds of Doll et al are attached to a resin via a linking group (L of the patent) through the carboxy moiety (R2 of the patent), specifically a carboxamide (reading on the instant X=NHR1). Referring to Process D of the patent, the piperazine ring structure is initially protected at both nitrogens, denoted P1 and P2. P1 and P2 can be CBZ and BOC (column 45, Example 58) or BOC and FMOC protecting groups (column 48, Example 18). These protecting groups inherently have the capacity of being removed with a metal reagent (BOC and CBZ) or base (FMOC). During the process of Doll et al, the first protecting group is removed and replaced by an R1 group and then the second protecting group is removed and replaced by carboxy group. The compounds are finally cleaved from the resin (see Process D). Specifically, compounds such as those depicted in Examples 21, 22, and 24-26 of Doll et al read directly on the claimed L1 and L2 groups (where Y1 and Y2 are CO or SO2).

B. Claims 1-6 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraph and further in view of Carroll et al, Dolle et al and Breitenbucher et al.

Doll et al teach the claimed method of making diazacycloalkylcarboxy derivatives as set forth supra.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

The reference does not specifically teach using the protecting groups set forth in claims 5 and 6.

However, the use of protecting groups was well established in the art at the time of filing and it would be routine to one of ordinary skill to choose the appropriate groups based on the reaction conditions being used. Also, each of the protecting groups of the claims were known to be used in the synthesis of the claimed compounds. For example, Carroll et al disclose a method of making cyclic diamino compounds via a solid phase methodology (see Scheme 1). Note in Table 1 that when the moiety denoted R3 is structure (1) the compounds read on those claimed, i.e. compounds having a piperazine ring structure with a carboxy substituent directly attached (in the compounds of Carroll et al, this corresponds to n=0). The compounds are attached to a resin via a linking group through the carboxy moiety, forming a carboxamide group (i.e. instant X group is NHR1). The piperazine ring structure is protected at both nitrogens, one with an alloc group and one with a BOC group. Also, in Dolle et al the use of alloc and BOC protecting groups in the solid phase synthesis of carboxy substituted piperazine compounds is taught. See Scheme 7 of Dolle et al (columns 21-22). Breitenbucher et al teach the synthesis of carboxamide piperazines on a solid support by use of a monosubtituted piperazine intermediate. Thus, depending on the desired chemistry one would choose the appropriate protecting groups.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to perform the method of Doll et al using any of a variety of well-known protecting groups. One would be motivated to specifically use alloc and FMOC since they are known to be orthogonal and are specifically known to be used in the solid phase synthesis of carboxy substituted piperazines as taught by each of the references.

C. Claims 7-13 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the preceding paragraph and further in view of Cody et al.

The references set forth in paragraph B teach the solid phase synthesis of carboxy substituted piperazines using one or two protecting groups. The references cited above lack the teaching of the attachment site as set forth in claim 7. However, solid phase synthesis of piperazines by linking a ring nitrogen to the resin via a linker was known at the time of filing. See the teachings of Cody et al in Scheme 10.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to perform the method of Cody et al to make any of the carboxy substituted compounds of Doll et al, Carroll et al, Dolle et al or Breitenbucher et al. One would be motivated to specifically use alloc and FMOC for the reasons set forth above and one would be motivated to link the compounds to the resin in a variety of ways in order to create a more diverse library. Diverse libraries are known to be advantageous in order to have more compounds to screen for activity, see, for example, the discussion in Carroll et al concerning libraries (page 3203).

D. Claim 14 lacks an inventive step under PCT Article 33(3) as being obvious over Doll et al in view of WO 98/58947.

Doll et al teach the claimed method of making diazacycloalkylcarboxy derivatives as set forth in paragraph A. The reference does not specifically teach the further reaction of the substituted piperazine to make the hydantoin as claimed.

However, such compounds were well known in the art at the time of filing and it was known to make such compounds from piperazine intermediates. See WO 98/58947, pages 75-77 and 158-159 of the reference. These compounds are known to increase the level of endogenous growth hormone, which is advantageous for a number of treatments (see Abstract).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to perform the method of Doll et al with further reaction to make the compounds of WO 98/58947 in order to have compounds to screen for more potent activity. Additionally, solid phase synthesis of the compounds of WO 98/58947 would have been obvious to one of ordinary skill as this methodology has a large number of advantages that are well recognized in the art.

E. Claims 1-14 meet the criteria set out in PCT Article 33(4) for industrial applicability because the compounds of the claims can be used as pharmaceutical or diagnostic agents.

---------- NEW CITATIONS ----------

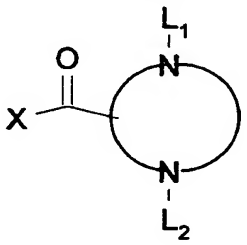
Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

CARROLL et al. Evaluation of a Structure-Based Statine Cyclic Diamino Amide Encoded Combinatorial Library against Plasmepsin II and Cathepsin D. Bioorg. Med. Chem. Lett. 17 November 1998, Vol. 8, pp. 3203-3206.

What is claimed is:

1. A method of preparing a diazacycloalkylcarboxy derivative of formula



wherein

X is NHR^1 or OH ;

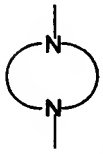
R^1 is H, aliphatic or aromatic;

L^1 and L^2 are independently $-Y^1R^2$ or $-Y^2R^3$;

R^2 and R^3 are independently aliphatic or aromatic;

Y^1 and Y^2 are independently -C(O)-, -C(O)O-, -C(O)NR^4- or $-SO_2$-;

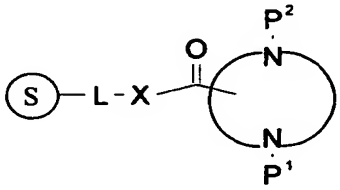
R^4 is H, aliphatic or aromatic; and



is a 5-8 membered diazaheterocyclyl ring,

comprising

(1) removing one of P^1 or P^2 from a resin-bound diprotected diazacycloalkylcarboxy derivative of formula



wherein

is a solid support;

L is absent or a linking group; and

one of P^1 and P^2 is a base-labile nitrogen protecting group and the other of P^1 and P^2 is a Metal-labile nitrogen protecting group,

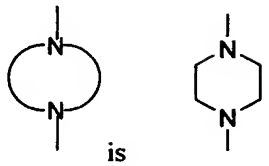
(2) introducing one of L^1 or L^2,

(3) removing the other of P^1 or P^2,

(4) introducing the other of L^1 or L^2 and

(5) isolating the diazacycloalkylcarboxy derivative.

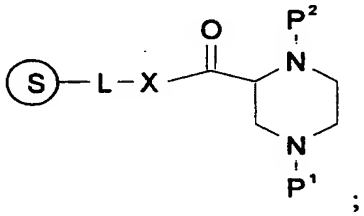
2. The method of claim 1 wherein



is

3. The method of claim 2 wherein P^1 is a base-labile nitrogen protecting group and P^2 is a metal-labile nitrogen protecting group.

4. The method of claim 3 comprising removing the base-labile nitrogen protecting group P^1 from a resin-bound diprotected diazacycloalkylcarboxy derivative of formula



;

(2) introducing the group L^1,

(3) removing the Metal-labile nitrogen protecting group P^2,

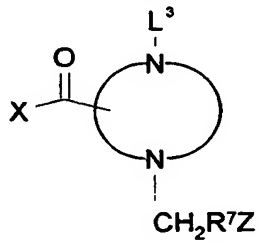
(4) introducing the group L^2 and

(5) isolating the diazacycloalkylcarboxy derivative.

5. The method of claim 4 wherein the Metal-labile nitrogen protecting group is selected from allyloxycarbonyl, 1-isopropylallyloxycarbonyl, cinnamyloxycarbonyl and 4-nitrocinnamyloxycarbonyl and the base-labile nitrogen protecting group is selected from 9-fluorenylmethoxycarbonyl, 9-(2-sulfo)fluorenylmethoxycarbonyl and 9-(2,2-dibromo)-fluorenylmethoxycarbonyl.

6. The method of claim 5 wherein the Metal-labile nitrogen protecting group is allyloxycarbonyl and the base-labile nitrogen protecting group is 9-fluorenylmethoxycarbonyl.

7. A method of preparing a diazacycloalkylcarboxy derivative of formula



wherein

X is OH or NR^5R^6

L^3 is $-Y^3R^8$;

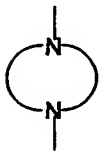
Y^3 is -C(O)-, -C(O)O- or $-SO_2-$;

Z is $-C(O)-OR^{10}$ or $-NR^{11}R^{12}$;

R^5, R^6, R^9, R^{10}, R^{11} and R^{12} are independently H, aliphatic or aromatic;

R^7 is aliphatic or aromatic;

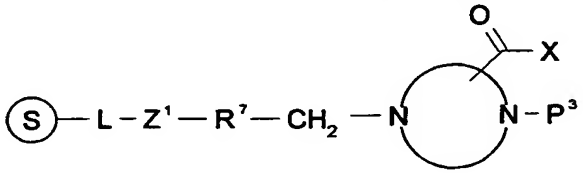
R^8 is aliphatic or aromatic; and



is a 5-8 membered diazaheterocyclyl ring,

comprising

(1) removing P^3 from a resin-bound diazacycloalkylcarboxy derivative of formula



wherein

is a solid support;

L is absent or a linking group;

P^3 is a nitrogen protecting group;

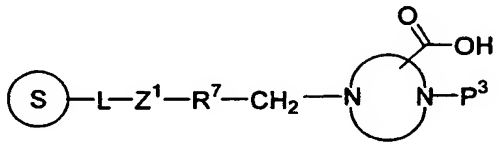
Z^1 is $-OC(O)-$ or $-OC(O)-NR^{13}-$; and

R^{13} is H, aliphatic or aromatic,

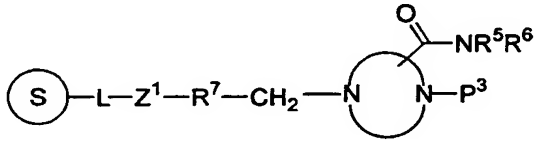
(2) introducing the group L^3,

(3) isolating the diazacycloalkylcarboxy derivative.

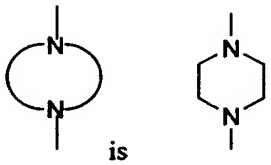
8. The process of claim 7 further comprising converting a resin- diazacycloalkylcarboxy derivative



to the resin-bound diazacycloalkylcarboxy derivative of formula



9. The method of claim 8 wherein



is

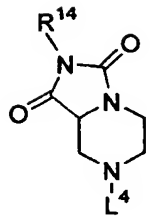
10. The method of claim 9 wherein P^3 is a base-labile nitrogen protecting group or a Metal-labile nitrogen protecting group.

11. The method of claim 10 wherein P^3 is a Metal-labile nitrogen protecting group selected from allyloxycarbonyl, 1-isopropylallyloxycarbonyl, cinnamyloxycarbonyl and 4-nitrocinnamyloxycarbonyl and or a base-labile nitrogen protecting group selected from 9-fluorenylmethoxycarbonyl, 9-(2-sulfo)fluorenylmethoxycarbonyl and 9-(2,2-dibromo)-fluorenylmethoxycarbonyl.

12. The method of claim 11 wherein P^3 is allyloxycarbonyl or 9-fluorenylmethoxycarbonyl.

13. The method of claim 12 wherein P^3 is allyloxycarbonyl.

14. A method of preparing a substituted hydantoin of formula



wherein

L^4 is Y^4R^{15};

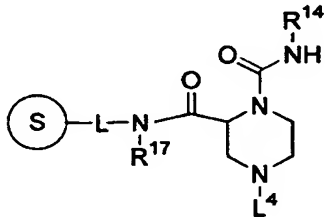
Y^4 is -C(O)-, -C(O)O-, -C(O)NR^{16}- or -SO_2-;

R^{14} is aromatic; and

R^{15} is aliphatic or aromatic; and

R^{16} is H, aliphatic or aromatic;

comprising reacting acid with a resin-bound diazacycloalkyl-2-carboxy derivative of formula



wherein

(S) is a solid support;

L is absent or a linking group; and

R^{17} is H, aliphatic or aromatic.